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Review Article

Immunological Aspects of Steroid Therapy

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THE PURPOSE of this communication is to review some of the basic principles which underlie the use of glucocorticoids and their various synthetic analogues in the therapy of different diseases, chiefly tuberculosis. Most of the material cited is extracted from *Resistance to Tuberculosis: Experimental Studies in Native and Acquired Defensive Mechanisms* published for the Commonwealth Fund by the Harvard University Press.[1] No attempt has been made to cover the vast literature on the subject.

Protective Effect of Adrenals Against Intoxications and Infections

More than 50 years ago Cushing[2] demonstrated that hypophysectomy increases the susceptibility of animals to poisons and infections. Lewis[3] found that adrenalectomy reduced the resistance of rats to intoxications. Perla and Marmorston-Gottesman[4] and Hartman and Scott[5] showed that certain extracts of the adrenal cortex afforded considerable protection to adrenalectomized animals against typhoid vaccines. Basing himself on the fundamental investigations of Cannon[6] on homeostasis, Selye announced the alarm reaction, the adaptation syndrome, and the role of the adrenal-pituitary system in response to stress.[7] After the isolation of cortisone, Robinson and his collaborators[8] and Kass[9] demonstrated that the lowered resistance to infection due to adrenalectomy can be overcome by physiological amounts of this glucocorticoid. There is thus no doubt that certain hormones of the adrenal cortex are essential in the protection against stress and infection.

Effects of Excess Corticosteroids on Resistance to Infections and Intoxications

The dramatic discovery of Hench et al[10] of the startlingly beneficial effects of cortisone and corticotropin (ACTH) on chronic rheumatoid arthritis stimulated a flood of investigations on the effects of corticosteroids on various biological processes, including infections and intoxications, which is still continuing throughout the world. Suffice it to state that *pharmacologic* doses of cortisone, hydrocortisone, and their different synthetic analogues markedly depress the resistance of various species, including man, against numerous bacterial, viral, fungal, and parasitic infections.[11,12] Particularly extensively investigated were the baneful effects of excess of these steroids on the progress of tuberculosis in various species[13,14] and, especially, on their mode of action in tuberculosis of inbred rabbits.[15-18] It is noteworthy that fatal tuberculosis can be caused by human-type tubercule bacilli in cortisone-treated rabbits.[16] This is similar to the fatal tuberculosis induced by attenuated tubercle bacilli, Rl and BCG, in silicotic guinea pigs. Cortisone can even make animals succumb to saprophytes.[19,20] Frenkel[21] presented evidence for the view that the endogenous steroids of the adrenal cortex permitted the *selective*, progressive multiplication of tubercule bacilli in this location which resulted in Addison's disease in man. It is clear, therefore, that excessive glucocorticoids reduce resistance to infection in general.

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On the other hand, there is ample proof that protection against endotoxin rises progressively with increasing doses of glucocorticoids.[22] Cortisone and corticotropin markedly reduce the febrile response to pyrogens.[23,24] Cortisone, cortisol, and corticotropin protect mice, rats, rabbits, and chick embryos against the lethal effects of endotoxins derived from a variety of bacterial species.[25-27] Cortisol induces hypothermia by a direct action of the steroid on the thermo-regulatory center of the hypothalamus.[28] The protective effect of cortisone against endotoxin depends on the concentration of the steroid in the circulation at the time of interaction of the endotoxin with the tissues.[26,29] There is no convincing evidence that cortisone protects sensitized cells against the cytotoxic effect of tuberculin.[30]

Mode of Action of Steroids on Resistance to Infection

Inflammation.—The anti-inflammatory effect of excess corticosteroids and their capacity to reduce capillary permeability is thoroughly established.[10,17,31] These effects of cortisol and its analogues depend largely on their sensitization of the arterioles to the pressor effect of norepinephrine [32,33] and the maintenance of vascular tone as demonstrated by Ebert [34] in tuberculosis by the rabbit ear chamber method. More recently, Grant, Palmer and Sanders [35] found that hydrocortisone in large quantities prevented the sticking of white blood cells to the vessel walls. It is clear that to the extent that these steroids retard the mobilization of phagocytic cells to the site of invasion of the pathogen, to that extent will the defensive mechanisms be impaired. Hence, this has been the most prevalent view of the mode of action of steroids in reducing resistance to infection [36] and their capacity to diminish injurious inflammatory responses to a variety of agents.

Carbohydrate and Protein Metabolism.—Cortisol and related compounds enhance gluconeogenesis, lower the utilization of carbohydrates, induce extensive nitrogen loss, and increase the total amount of fat at the expense of protein.[37,38] The metabolic properties of these steroids are important in the functions of phagocytic and other cells concerned in resistance to infection.

Antibody Formation.—Lympholysis and suppression of lymphopoiesis [39] are among the constant effects of steroid administration. This is probably responsible for the depression of antibody formation as demonstrated by numerous observers.[40,41,11] There is no agreement on the effect of steroids on acquired resistance. Mogabgab and Thomas [42] found no reduction, while Solotorovsky et al [43] and Frenkel [44] have produced evidence indicating reduction of acquired resistance in the presence of circulating antibodies. Furthermore, the antianabolic growth inhibiting properties of glucocorticoids and their effect on connective tissue constituents and fibroblast formation interfere with the healing process.[45,46] Considering that in tuberculosis the acquired resistance is superimposed on the native cellular resistance and that there is considerable evidence (to be considered below) that glucocorticoids alter their native functions, it is not surprising that occasional reactivation of latent tuberculosis occurs after steroid treatment of chronic rheumatoid arthritis.[47]

Steroids and the Functions of Phagocytic Cells

Phagocytosis.—The energy for phagocytosis is derived from carbohydrate metabolism as determined by Karnovsky.[48] Since cortisol lowers the utilization of carbohydrates, it was not unexpected when Martin et al [49A] found that cortisol reduces the glycolytic activity of leucocytes. On the other hand, both endotoxin and insulin increase it.[49B] Moreover, not only do steroids reduce the mobilization of phagocytes in vivo by virtue of their anti-inflammatory effect but they also counteract the endotoxin-induced stimulation of migration of leucocytes in vitro [50] and thus diminish the efficiency of the phagocytic process. Cortisone blocks the removal of chromium phosphate from the circulation by the Kupffer cells of the liver. Endotoxin counteracts this effect [51] by increasing the glycolytic activity of the macrophages,[52] just as insulin can reverse the decrease of carbohydrate metabolism and the rate of protein catabolism brought about by cortisol.[38] The various hormones may act synchronously but not necessarily synergistically on the metabolic processes. Furthermore, glucocorticoids activate the production of pyruvate and oxalacetate and thus make up

for the loss of energy induced by these steroids resulting from their reduction of glycolysis. Hence, pharmacologic doses of steroids do not uniformly affect phagocytosis.[53]

Steroids and Enzymes of Mononuclear Phagocytes.—Besides lowering glycolysis, cortisone also depresses the acid phosphatase and dehydrogenase activity of mononuclear phagocytes.[54] On the other hand, the administration of endotoxin is followed within 48 hours by an elevation of the acid phosphatase activity of the reticuloendothelial cells.[55] Similarly, the activity of this enzyme in homogenates of mononuclears cultured in vitro is greater in those derived from BCG vaccinated than in cells from normal rabbits.[56] It is noteworthy that both endotoxin administration and BCG vaccination, contrary to cortisone, enhance nonspecific resistance to infections after a certain interval.

Lysosomes and Cortisone.—de Duve and his collaborators [57,58] demonstrated the presence within rat liver cells of particles, lysosomes, enclosed in a lipoprotein membrane which contain a variety of hydrolases such as cathepsin, acid phosphatase, beta glucoronidase, desoxyribonuclease and other enzymes active at an acid pH. Similar lysosomes have been identified in the granules of polymorphonuclear leucocytes by Cohn and Hirsch.[59] These organelles contain, in addition to the hydrolases, the bactericide "phagocytin" of Hirsch [60] and lysozyme. Following phagocytosis there is an increase in lactic acid production which ruptures the lysosome membrane of the polymorphonuclear granules and releases the enzymes and bactericidin into the vacuoles about the ingested bacteria.[61] The microorganisms susceptible to destruction by phagocytin are thus eliminated. Lysosomes have also been demonstrated by Cohn and Wiener [62] within mononuclear phagocytes, especially in alveolar macrophages. These lysosomes contain acid phosphatase, lysozyme, lipase, and cathepsin. Upon phagocytosis these organelles release their enzymes in a manner similar to that which overtakes the granules of polymorphonuclears.

While hydrocortisone inhibits the release of lysosomal proteases from rat liver lysosomes,[63] degranulation of exudative polies after ingestion of streptococci or zymosan particles is not affected by large doses of cortisone given to the donor rabbit of these leucocytes.[64] Nor is there any indication that cortisone increases the stability of the lysosome membrane of mononuclear phagocytes. However, there is clear evidence that cortisone protects against endotoxemia and shock [65] by counteracting the solubilization of the lysosomal membrane due to endotoxin.[66] This stabilizing effect of steroids on the lysosomal membranes may also play a role in the anti-inflammatory effects of the corticoids in certain tissues by reducing in vivo autolysis, a potent stimulus for inflammation.[67]

Cortisone and Inactivation of Materials Ingested by Mononuclear Phagocytes.—Hirsch and Church [64] found no difference between the killing capacity of certain staphylococci and enteric bacteria ingested by granulocytes derived from cortisone-treated and untreated rabbits, and no effect of the steroid on the content of their antimicrobial agents such as lysozyme, phagocytin, and histone. Yet, there are a number of observations which suggest that cortisone reduces the digestive or inactivating capacity of mononuclear phagocytes for various microbes and other materials. Two weeks after the quantitative inhalation of human type tubercle bacilli by susceptible rabbits, the rare minute mononuclear primitive foci in the untreated rabbits contained but few visible and living bacilli. At the same time, the much more numerous and much larger mononuclear accumulations in the cortisone-treated rabbits were swarming with living bacilli.[16] Cortisone retards the maturation of epithelioid cells.[17] It has been found repeatedly, under various conditions, that the maturation of these cells is associated with the inhibition of proliferation and disposal of tubercle bacilli.[1] These observations would suggest that it is not the paucity of mobilization of phagocytes that is solely responsible for the accumulation of the intracellular bacilli but also that cortisone reduces the innate capacity of the mononuclears of the treated rabbits to inactivate the ingested bacteria. There is no evidence that cortisone enhances the virulence of the bacilli. Thomas [68] showed that cortisone caused a fatal streptococcal septicemia within 24 hours after inoculation, from which untreated rabbits recovered in a few hours. This can hardly be accounted for by the failure of antibody formation or the depression of the inflammatory process. Cortisone impairs the reticuloendothelial cell inactivation of endotoxin,[69] of protozoa,[44] of autologous eryth-

rocytes,[70] and of phagocyted protein complexes.[71] Finally, it was demonstrated by Holden and Adams [72] that Earle L cells infected with vaccinia virus and cultivated in a medium containing hydrocortisone underwent more severe cytopathic changes and yielded a more marked increase of infective virus than such cells grown in the absence of the hormone. This is similar to the high mortality of cortisone-treated mice and rabbits inoculated with the same virus. These data indicate that glucocorticoids fundamentally alter the behavior of certain mononuclear cells toward ingested microbial agents apart from their anti-inflammatory effects.

Cortisone and the Action of Antimicrobials

There is some evidence that adequate cellular function is necessary for the full antimicrobial action of streptomycin in tuberculosis.[73] Long [74] has emphasized the supporting structure of immunity in the therapy of the disease and Jawetz [75] reported that nontoxic cortisone treatment reduced the efficacy of the bacteriostatic action of chlortetracycline (Aureomycin) on *Klebsiella* infection of mice.

Steroid Therapy and Clinical Experience

The above analysis of the mode of action of corticosteroids in resistance to infection is based on the use of *pharmacologic* doses of glucocorticoids in experimental animals. Under these conditions there is almost universal agreement that these steroids greatly increase the susceptibility of many species to a variety of infections. However, in man the prolonged administration of *therapeutic* quantities of corticotropin and cortisone in rheumatoid arthritis and disseminated lupus erythematosus did not exert an unusual effect on the incidence or severity of infections, although symptoms were masked in some cases.[76]

On the basis of the anti-inflammatory effects of corticosteroids a number of clinical investigations have established that the addition of these steroids to the antimicrobial treatment of pulmonary tuberculosis results in a more rapid clinical improvement and an earlier resolution of roentgenographic changes.[77] In the same category are the widely accepted beneficial effects of steroid therapy in hypersensitivity reactions of various origins. While some cases of latent tuberculosis have been reactivated by steroids, Alemquer [77] and Spink [47] have presented evidence which suggests that in certain infections, including tuberculosis, steroids in combination with appropriate antimicrobials are definitely indicated. Where severe inflammation involves crucial organs such as the nervous system, the heart, and the lungs, the anti-inflammatory effect of the steroids may be life-saving. In the most recent study of life-threatening tuberculous cases [78] steroid therapy showed no significant advantage. However, in these instances inanition and respiratory failure due to retention of tracheobronchial secretion were considered as prominent in the fatal issue.

On the other hand, in line with the protective effects of adrenal steroids against endotoxin [22] and shock,[65] Spink [47] found that large doses of these steroids administered intravenously for short intervals contributed to the recovery of patients with acute bacterial shock and vascular collapse due to endotoxins and other conditions.

Summary

Physiological quantities of certain glucocorticoids are essential for the protection of man and animals against infections and intoxications. Pharmacologic doses of these steroids markedly reduce the resistance of numerous species, including man, to a variety of infections. This is due (1) to their anti-inflammatory effects which inhibit the mobilization of phagocytes to the site of invasion of the pathogens; (2) to their anti-anabolic effects, in general, and on lymphocytes and connective tissue constituents, in particular, which interfere with the healing process. (3) The suppression of antibody formation which follows excess steroid administration has not been found to play a decisive role in the increased susceptibility which results from this hormone treatment. (4) There is some evidence that such steroid treatment alters some metabolic and hydrolytic functions of certain macrophages which may be active in maintaining resistance against infections. (5) The effect of these steroids on the stability of the lysosomal membranes within these cells which affect the release of hydrolytic enzymes present in these organelles and induce autolytic processes is discussed. Which of these altered functions and structures

are partly responsible for the enhancement of intracellular accumulation of various pathogens is not known.

Clinical experience suggests that therapeutic doses of steroids in allergic diseases does not materially increase the incidence of infections. These corticosteroids, even in excess, protect against pyrogens and the lethal effects of endotoxins and shock. The judicious use of steroids may be life-saving in certain types of hypersensitivity reactions associated with excessive cellular inflammation involving crucial organs.

Generic and Trade Names of Drugs

Corticotropin—*Acth, Acthar, Corticotropin.*
Chlortetracycline—*Aureomycin*

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NEW CONCEPT OF HEALTH

It is interesting that the word unemployment did not exist until late in the nineteenth century. It was simply not realized that large numbers of men without work constituted a social phenomenon. The only applicable words in use were words such as idleness, laziness and hard luck—words expressive of the individual's condition and character, not of the social framework within which his life was lived. Once the phenomenon of unemployment was discerned, analyzed and given a name, the possibility was open for dealing with it as a community problem. Something comparable to this transformation has occurred in health.—HECKSCHER, H.: Medicine and Society, *New England J Med* 262:19 (Jan 7) 1960.